

Proposed Decision Memo for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N)

Decision Summary

On August 1, 2007, we initiated the national coverage determination (NCD) process by opening a tracking sheet for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N). CMS proposes not to expand the colorectal cancer screening benefit to include coverage of this test because the FDA has determined that the only commercially available test, PreGen-Plus™, requires premarket review. We will consider a request for reconsideration when a commercially available stool DNA test has been cleared or approved by the FDA.

We are requesting public comments on this proposed determination pursuant to Section 1862 (I) of the Social Security Act (the Act). After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File: CAG-00144N
Screening DNA Stool Test for Colorectal Cancer

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Subject: Proposed Coverage Decision Memorandum for Screening DNA Stool Test for Colorectal Cancer

Date: January 30, 2008

I. Proposed Decision

On August 1, 2007, we initiated the national coverage determination (NCD) process by opening a tracking sheet for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N). CMS proposes not to expand the colorectal cancer screening benefit to include coverage of this test because the FDA has determined that the only commercially available test, PreGen-Plus™, requires premarket review. We will consider a request for reconsideration when a commercially available stool DNA test has been cleared or approved by the FDA.

We are requesting public comments on this proposed determination pursuant to Section 1862 (I) of the Social Security Act (the Act). After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

II. Background

For many years, screening for colorectal cancer (CRC) with fecal occult blood tests (FOBTs) has been recommended by various professional organizations including the U.S. Preventive Services Task Force (USPSTF available at <http://www.ahrq.gov/clinic/uspstf/uspscolo.htm>). Specifically, the USPSTF noted "good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer" (USPSTF, 2002). Medicare currently covers 2 stool hemoccult based tests: the guaiac test and the immunochemical test. The advantages of these tests over other CRC screening tests include the relative simplicity, non-invasive nature, wide availability and cost-effectiveness. The main disadvantage is the variable sensitivity of a single stool hemoccult test, estimated at 40% for a guaiac test (USPSTF, 2002).

Recently, mutant (abnormal) (deoxyribonucleic acid (DNA)) in the stool has been targeted as another modality for CRC screening. One such test, PreGen-Plus™ Version 1.1 by Exact Sciences, has been on the market for several years. PreGen-Plus™ Version 1.1 consists of a panel of 23 individual tests to detect 21 specific mutations in the APC, K-ras and p53 genes, a marker for microsatellite instability known as Bat-26, and a marker known as DNA Integrity Assay (DIA®), Exact Sciences 2004 available at <http://www.mi3.com/pressreleases/2004.12.22.Exact.pdf>). In August 2007, CMS accepted a formal request from Exact Sciences for Medicare coverage of stool DNA testing for CRC screening in average risk individuals. The requestor asks CMS to cover their test every 5 years as an alternative to a screening colonoscopy that may be covered every 10 years or as an alternative to a screening flexible sigmoidoscopy that may be covered every 4 years for such individuals as provided in 42 CFR 410.37(e) and (g). See, also § 1834(d) of the Act.

III. History of Medicare Coverage

The Balanced Budget Act of 1997, Public Law No. 105-33, § 4194 (1997), established coverage for screening colorectal cancer procedures under Medicare Part B, effective January 1, 1998. Medicare currently covers (1) annual FOBTs, (2) flexible sigmoidoscopy every 4 years, (3) screening colonoscopy for persons at average risk for colorectal cancer every 10 years¹, or for persons at high risk for colorectal cancer every 2 years², (4) barium enema every 4 years as an alternative to flexible sigmoidoscopy or colonoscopy, and (5) other procedures the Secretary finds appropriate based on consultation with appropriate organizations. Coverage of these screening exams was implemented in regulations through a final rule that was published on October 31, 1997 (Federal Register Notice 10/31/1997, Vol. 62, No. 21, 59079-59082, 59100-59101), and was effective January 1, 1998.

In the Physician Fee Schedule Final Rule for 2003, CMS amended the FOBT screening test regulation definition in CFR 410.37 (a) (2) to provide that it could include coverage of either (1) a guaiac-based FOBT, or (2) other tests as determined by the Secretary through a national coverage determination (Federal Register Notice 12/31/2002, Vol. 67, No.251, 79966, 80040). On November 4, 2003, CMS issued a final Decision Memorandum indicating that effective with that date Medicare would cover a screening immunoassay FOBT on an annual basis as an alternative to the guaiac-based FOBT.

In the Physician Fee Schedule Final Rule for 2003, CMS also amended the colorectal cancer screening test regulation in 42 CFR 410.37 (a) (1) (v) to provide that in addition to the screening test options already covered under the regulation, it could include coverage of additional colorectal cancer screening tests through issuance of a national coverage determination (Federal Register Notice 12/31/2002, Vol. 67, No. 251, 79966, 80040).

Tests performed as a CRC screening test are also frequently used as a diagnostic test. This NCD does not address the use of stool DNA testing as a diagnostic test.

Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category under part A or part B as a prerequisite to Medicare coverage under the fee-for-service program. Congress has specifically authorized coverage of certain screening tests under part B of the Medicare program and has consistently made necessary conforming changes in order to ensure that payments are made. Colorectal Cancer Screening Tests have a benefit category under §1832, §1861(s)(2)(R) and §1861(pp) of the Act. Specifically, CMS is using the national coverage determination authority under section 1861(pp)(1)(D) and 42 CFR 410.37(a)(1)(v) to determine whether the scope of the CRC screening benefit should be expanded to include coverage of the DNA stool test.

IV. Timeline of Recent Activities

August 1, 2007 Request for consideration of EXACT Sciences' PreGen-Plus™ screening DNA stool test produce accepted by Coverage and Analysis Group.

September 1, 2007 Initial 30-day public comment period closes.

November 15, 2007 CMS sends letter to EXACT Sciences inquiring about the marketability of their test, in light of FDA's Warning Letter of October 11, 2007, indicating serious regulatory problems with their test (Appendix A).

December 14, 2007 CMS meets with EXACT Sciences to discuss the FDA's Warning Letter, including when the FDA's concerns might be resolved and their impact on CMS' NCD process.

December 20, 2007 CMS receives letter from EXACT Sciences requesting that they be allowed to withdraw their test from the NCD evaluation process pending the resolution of the FDA's regulatory concerns.

January 9, 2008 CMS posts a technology assessment, including a cost effectiveness analysis for use of this test as a screening test, which was requested from the Agency For Healthcare Research and Quality.

January 30, 2008 Proposed decision memorandum posted; 30-day comment period begins.

V. FDA Status

The FDA would consider a test for DNA detection in stool intended to replace fecal occult blood detection to be a class II device (moderate risk), which would require a Premarket Notification (510(k)) to the FDA prior to marketing. Such a test intended to replace colonoscopy would represent a device with a new intended use and would be considered a class III device (high risk) by the FDA. Class III devices require premarket approval by the FDA prior to marketing.

On October 11, 2007 EXACT Sciences received a warning letter from the FDA that stated that the PreGen-Plus™ test is a medical device that requires FDA clearance or approval prior to marketing and is currently being marketed in violation of the Federal and Food Drug and Cosmetic Act (Appendix A). To date, EXACT Science's PreGen-Plus™ test has not been cleared or approved by FDA.

VI. Evidence

A. Introduction

In general, for a test to be considered a good screening test, a number of factors must be evaluated, including the sensitivity, specificity, simplicity, cost, safety, availability and acceptability. CMS reviewed the definitions of these characteristics and their application to colorectal cancer screening in 2003 in the context of the national coverage determination on screening immunoassay fecal occult blood test (Available at <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=87>). Given the existing CRC screening options, experts recommend choosing a specific strategy for a given patient based upon patient preferences, medical contraindications, patient adherence and available resources for testing and follow-up (USPSTF 2002).

In addition to performance characteristics, morbidity and mortality have been studied as outcomes of colorectal cancer screening. For example, FOBT screening has been shown to improve mortality (USPSTF 2002). Since a number of screening tests are available and covered for colorectal cancer, how a new test should be used and how it fits into the current recommendations for screening also should be considered.

Specifically for stool DNA testing, this determination focused on the only test (PreGen-Plus™ Version 1.1) that was commercially available when we initiated the analysis. PreGen-Plus™ Version 1.1 was also the test panel that was used in the published studies. PreGen-Plus™ Version 2.0 is reportedly in development but is not considered in this decision.

Literature Search

CMS searched PubMed from 2000 to present. General keywords included stool/fecal DNA and colorectal cancer. Publications that presented original data on screening with DNA testing were considered. Abstracts, animal studies and non-English publications were excluded.

B. Discussion of evidence reviewed

1. External technology assessments

Zauber AG, Lansdorp-Vogelaar I, Wilschut J, et al. Cost-effectiveness of DNA stool testing to screen for colorectal cancer. AHRQ Technology Assessment Program 2007
This can be found (at <http://www.cms.hhs.gov/mcd/viewtechassess.asp?id=212>) .

In 2007, Zauber and colleagues reported the results of an analysis “to assess the cost-effectiveness of screening for CRC with the DNA stool test in comparison to the currently recommended CRC screening strategies.” The cost-effectiveness analysis was based upon simulations using 2 well accepted, validated models: the MISCAN-Colon (Microsimulation model of the Memorial Sloan-Kettering Cancer Center and ErasmusMC) and SimCRC (Microsimulation model of the University of Minnesota and Massachusetts General Hospital). The models incorporate literature-derived estimates of sensitivity and specificity of the DNA stool test for detecting adenomas by size and for CRC. They also incorporate direct medical costs estimated using current CMS reimbursement rates, an estimate for the cost of the DNA stool test, and derived beneficiary costs. The analysis used a modified societal perspective and included sensitivity and threshold analyses. The authors concluded: “These results suggest that screening for CRC with the DNA stool test version 1.1 does provide a benefit in terms of life-years gained compared with no screening but the cost, relative to the benefit derived and to the availability and costs of other CRC screening tests, would need to be in the range of \$34-\$60 to be a non-dominated option. Only if significant improvements for the DNA stool test characteristics or relative adherence with DNA stool testing compared with other available options can be demonstrated, will stool DNA testing at the current costs of \$350 be cost-effective. These estimates are based on a third-party payer analysis on an unscreened 65-year old cohort. Threshold costs are similar for a 50-year old cohort, but can be somewhat higher from a modified societal perspective (\$88 to \$134 for 5-yearly testing and \$73 to \$116 for 3-yearly testing).”

Blue Cross Blue Shield Technology Evaluation Center. Fecal DNA special report: Analysis for colon cancer screening. BCBS TEC Assessment Program 2006; Volume 21, No. 6 (at http://www.bcbs.com/betterknowledge/tec/vols/21/21_06.pdf).

In 2006, the Blue Cross Blue Shield Technology Evaluation Center (BCBS TEC) published an assessment to “provide information relevant to the evaluation of fecal DNA screening for colon cancer in asymptomatic patients at average risk.” The special report addressed: “the current context of existing and emerging screening tests for colorectal cancer, including current published recommendations; the molecular basis for fecal DNA screening and the commercially available fecal DNA screening test, PreGen-Plus™; direct and indirect evidence comparing the performance of PreGen-Plus™ testing to other methods of colon cancer screening; evidence regarding the likelihood of compliance with fecal DNA screening; and available cost-effectiveness analyses of fecal DNA screening.” One study (Imperiale 2004) was evaluated for clinical utility of fecal DNA screening. The TEC concluded: “Fecal DNA testing is a noninvasive colorectal cancer screening technology that may eventually offer sensitivity for cancer closer to that of colonoscopy than that of conventional, guaiac-based FOBTs. Although the impact of fecal DNA screening on cancer morbidity and mortality has not yet been studied, it seems reasonable to assume that attaining sensitivities equal to or better than that of FOBT would result in similar or improved outcomes. However, several questions remain before fecal DNA screening can be widely recommended:

- Can sensitivity for large adenoma be significantly increased compared to FOBT?
- Can false-positive rates be maintained appropriately low for a screening program?
- What is the final configuration of the PreGen-Plus™ test and what are its published performance characteristics in an average-risk screening population?
- What is the optimal screening interval?
- Which patients should not be screened with fecal DNA testing?
- Does the test improve compliance with colorectal cancer screening?
- Is the test cost-effective?”

2. Internal technology assessment

Ahlquist DA, Skoletsky JE, Boynton KA, et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. Gastroenterology 2000;119:1219-1227.

In 2000, Ahlquist and colleagues reported the results of a retrospective case series of 61 patients to explore "the feasibility of a stool assay panel of selected DNA alterations in discriminating subjects with colorectal neoplasia from those without." Stool specimens were "selected from a freezer archive to yield subject groups with verified colorectal adenocarcinoma, colorectal adenomas ≥ 1.0 cm, and colonoscopically normal colons." Stool specimens were "collected within days before cathartic preparation for a scheduled colonoscopy, which served as the criterion standard." Specimens were frozen at -80°C . Specimens were then sent to Exact Sciences and tested for 15 point mutations on the K-ras, APC, and p53 genes, Bat-26 marker of microsatellite instability.

Of the 61 patients, 22 had colorectal cancer, 11 had adenomas and 28 were normal on colonoscopy. The authors reported: "Analyzable human DNA was recovered from all stools. Sensitivity was 91% (95% confidence interval, 71%-99%) for cancer and 82% (48%-98%) for adenomas >1 cm with a specificity of 93% (76%-99%). Excluding K-ras from the panel, sensitivities for cancer were unchanged but decreased slightly for adenomas to 73% (39%-94%), while specificity increased to 100% (88%-100%)." They concluded: "Assay of altered DNA holds promise as a stool screening approach for colorectal neoplasia. Larger clinical investigations are indicated."

Tagore KS, Lawson MJ, Yucaitis JA, et al. Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia. Clinical Colorectal Cancer 2003;3:47-43.

In 2003, Tagore and colleagues reported the results of a case series of 292 patients to "provide an estimate of the sensitivity and specificity of a multitarget assay panel (MTAP) of stool DNA changes." Stool specimens were obtained before colonoscopy from 80 patients with colorectal neoplasia and 212 with normal colonoscopy results or small polyps only. Stool specimens were frozen, sent to Exact Sciences for DNA analysis, and tested for 21 mutations in the K-ras, APC and p53 genes, BAT-26 marker and a marker of disordered apoptosis (DIA®).

Of the 80 patients, 52 had invasive colorectal cancer and 28 had advanced adenomas. The authors reported that the MTAP "detected 33 of 52 patients (63.5%, 95% confidence interval [CI], 49.0%-76.4%) with invasive colorectal cancer" and 16 of 28 patients with advanced adenomas (57.1%). Of the controls, the MTAP was "positive in 8 of 212 subjects for whom colonoscopy was either completely negative or revealed only small polyps, yielding a specificity of 96.2% (95% CI, 92.7%-98.4%)." The authors concluded: "The MTAP identified 49 of 80 patients with advanced colorectal neoplasia (61.2%; 95% CI, 49.7%-71.9%), including patients with invasive cancer (33 of 52; 63.5%) and advanced adenomas (16 of 28; 57.1%). Compared with historic FOBT results for single-point-in-time studies, the detection of DNA abnormalities in stool appears to be substantially more sensitive, with comparable specificity. Importantly, the sensitivity for early stage lesions (AJCC stages 0, I, and II) and other advanced adenomas appears to be similar to that for late-stage lesions (AJCC stage III/IV), suggesting that this modality might be more effective in detecting the lesions that are most curable. The MTAP as a noninvasive screening option may be useful in bringing a larger segment of the population into screening and help screen those patients who can benefit most from colonoscopy."

Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. New England Journal of Medicine 2004;351:2704-14.

In 2004, Imperiale and colleagues reported the results of a cross sectional study of 2507 individuals to compare “an approach that identifies abnormal DNA in stool samples with the Hemoccult II fecal occult-blood test in average-risk, asymptomatic persons 50 years of age or older.” There were no other inclusion criteria listed. Exclusion criteria included prior gastrointestinal bleeding, colorectal cancer, polyps and colonoscopy within 10 years. The fecal DNA test by Exact Sciences (PreGen-Plus™) was used. Colonoscopy was the reference standard test for cancers and polyps. Of the 5486 individuals enrolled, 4404 completed stool tests and colonoscopy. Of these, 2507 were included in the analysis (23 patients with advanced adenomas were excluded, as well as 1874 randomly selected patients with minor polyps or no polyps). For the 2507 patients analyzed, mean age was 69.5 years. Men comprised 44.5% of the analyzed group.

The authors reported the following results: “The fecal DNA panel detected 16 of 31 invasive cancers, whereas Hemoccult II identified 4 of 31 (51.6 percent vs. 12.9 percent, $P=0.003$). The DNA panel detected 29 of 71 invasive cancers plus adenomas with high-grade dysplasia, whereas Hemoccult II identified 10 of 71 (40.8 percent vs. 14.1 percent, $P<0.001$). Among 418 subjects with advanced neoplasia (defined as a tubular adenoma at least 1 cm in diameter, a polyp with a villous histological appearance, a polyp with high-grade dysplasia, or cancer), the DNA panel was positive in 76 (18.2 percent), whereas Hemoccult II was positive in 45 (10.8 percent). Specificity in subjects with negative findings on colonoscopy was 94.4 percent for the fecal DNA panel and 95.2 percent for Hemoccult II.”

They concluded: “Although the majority of neoplastic lesions identified by colonoscopy were not detected by either noninvasive test, the multitarget analysis of fecal DNA detected a greater proportion of important colorectal neoplasia than did Hemoccult II without compromising specificity.” In this report, it was unclear why a sample of patients was selected for analysis.

Syngal S, Stoffel E, Chung D, et al. Detection of stool DNA mutations before and after treatment of colorectal neoplasia. Cancer 2006;106:277-283.

In 2005, Syngal and colleagues reported the results of a case series of 91 patients to “1) define the sensitivity of a refined multitarget assay panel (MTAP) for detecting DNA abnormalities in stool specimens collected from a large cohort of individuals with colorectal carcinoma or advanced adenomas; and 2) to prospectively examine whether the mutations detected in stool DNA before treatment persist after surgical resection and/or adjuvant therapy.” Patients with “newly diagnosed colorectal carcinoma or advanced adenoma measuring ≥ 1 cm” were eligible. Stool specimens were collected at least 14 days after endoscopy but before surgery and/or chemoradiation. Specimens were transported from the patients’ home to Exact Sciences directly. The DNA assay consisted of 23 markers [21 mutations in the K-ras, APC, p53 genes, BAT-26 marker and a marker of disordered apoptosis (DIA®)].

A total of 135 patients were enrolled but 8 patients were nonevaluable and 36 provided inadequate specimens. The authors reported: “Overall, 49 of 91 individuals (54%) tested positive with the MTAP test. The sensitivity of the MTAP test was 63% for invasive tumors compared with 26% for AA (advanced adenomas). Individuals whose lesions had a more advanced TNM stage or were located distal to the splenic flexure were significantly more likely to have a positive MTAP test. Of the 79 samples collected at 1–3 months after surgical resection of the neoplasm, 14 (18%) had a positive MTAP result, 12 of which were positive for DIA only. Of those collected at 6–9 months of follow-up, 5 of 72 (7%) tested positive on the MTAP panel.” They concluded: “Although many samples collected 1–3 months after surgical resection of the colorectal neoplasm tested positive on the MTAP, most were negative by 6–9 months, indicating that stool DNA abnormalities disappear after treatment of the neoplastic lesions. Surgery and chemoradiation appear to induce transient DIA abnormalities that may be independent of the presence of neoplasia.”

3. MEDCAC

No MEDCAC was held for this topic.

4. Evidence-based guidelines

We have reviewed the USPSTF recommendations on screening for colorectal cancer in average risk populations and they are silent on the use of the DNA stool test for that purpose.

5. Professional Society Position Statements

An expert panel convened by the American Gastroenterological Association examined stool DNA screening in 2003 and commented that “this approach is promising.” However, they noted that the effectiveness data were not well enough established to be recommended (Winawer et al, 2003).

As indicated in its 2006 “ASGE Guide: Colorectal Screening and Surveillance,” the American Society for Gastrointestinal Endoscopy states that: “Studies evaluating virtual colonoscopy and fecal DNA testing for CRC screening have yielded conflicting results and therefore cannot be recommended.”

6. Public Comments

CMS received 154 comments during the initial 30-day public comment period. Six were from medical professional societies and other professional organizations and of the remaining 148, 8 of those included references and citations to clinical evidence.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will not be made available to the public. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

Comments from Professional Societies and Organizations

CMS received comments from the following: American Cancer Society Cancer Action Network (ASC CAN), American Gastroenterological Association (AGA), American Society for Gastroenterologists (ASGE), College of American Pathologists (CAP), Blue Cross and Blue Shield Association (BCBSA), and National Black Nurses Association (NBNA).

Three commenters (AGA, ASGE, and BCBSA) recommended that CMS not proceed with an NCD allowing coverage of the stool DNA screening test (PreGen-Plus, version 1.1) as an alternative to screening colonoscopy that may be covered every 10 years as provided under the Medicare law and regulations. All three of these commenters indicated that while some future version of the test might be demonstrated to have performance characteristics equal to or better than alternative noninvasive screening tests for colorectal cancer, this was not the case with this version of the test, based on current medical scientific literature. Specifically, BCBSA included a copy of the results from its Technology Evaluation Center (TEC) assessment that was issued in August 2006 and indicated that several unanswered questions now prevent a recommendation for coverage, including: final test configuration; sensitivity and false positive rate in an average-risk screening population; and lack of cost-effectiveness. Two commenters (CAP and NBNA) supported coverage of the test without any references to clinical evidence, but CAP expressed concern that the proposed coverage was limited to the PreGen-Plus test, version, 1.1. CAP stated that it did not believe that version 1.1 of the assay was so unique that coverage should be limited to it alone, and it suggested that CMS should "include coverage of all valid stool DNA tests that are performed in CLIA certified laboratories." One commenter (ASC CAN) stated that it would like to provide comments on the appropriateness of the test, but indicated that it would be premature to do that in view of the fact that the Society was currently updating its colorectal cancer screening guidelines and would soon be issuing them.

Comments with Evidence

Comments with evidence are public comments in which the commenter included references to publicly available information. There were 8 of these comments that were not previously summarized in the above section for professional societies and organizations. Five of these commenters supported coverage of the new screening test; three were non-supportive. Articles and information provided as evidence were considered in developing this proposed decision memorandum.

Test Performance

All commenters in favor of coverage referred to the Imperiale study (5,486 patients from 80 sites) comparing fecal DNA testing to guaiac-based FOBT reported in 2004. Several of these commenters emphasized that in this large study the sensitivity of the stool DNA test was demonstrated to be four times better (52%) than the sensitivity of the FOBT (13%). Several of these commenters also cited a more recent study by Itzkowitz that describes an even better (approximately 88%) sensitivity of an "improved version of the stool DNA test," referred to as PreGen-Plus™ Version 2. Additionally, one commenter noted that several studies have shown a clear patient preference for DNA-detection over traditional methods of screening for colorectal cancer.

Commenters opposed to coverage raised questions concerning the test performance of the PreGen-Plus™, based on the results of the evidence they had reviewed, including two large studies that have been performed on the test (Imperiale 2004 and Itzkowitz 2007). One commenter stated that “Neither of the two large multicenter studies described above of PreGen Plus’ performance characteristics in large average risk populations has shown sensitivity or specificity data robust enough to justify its inclusion as a new screening option on a five-yearly basis.” The commenter goes further to indicate that “Fecal DNA tests need to be shown in head to head comparison studies to have equal or superior performance characteristics to the immunochemical test, a much cheaper and easily performed test alternative already approved by CMS.”

Final Test Configuration

Five commenters opposing coverage expressed concern regarding the maturity of the stool DNA test technology based on the changes that have been made in it in the past five or six years. One commenter noted that “Published data and authoritative reviews of the sole commercially available DNA fecal test (PreGen-Plus, Exact Sciences) indicate that the test itself is a work in progress and its development and component markers are continually being changed in an effort to achieve acceptable performance characteristics.” A second commenter noted that “The PreGen-Plus test as originally reported by Imperiale et al. included a 21 mutation multitarget panel as well as a test for long chain DNA (L-DNA). The test subsequently described as “Version 2” is quite different, having seemingly dropped the mutation panel, improved the test for L-DNA and added a marker for vimentin methylation. This leads one to conclude that the data from the first version are not necessarily relevant to the second (even though the name is common) as the test technology has changed so much.” Another commenter pointed out that the CMS tracking sheet specifies that PreGen-Plus™ Version 1.1 is the test in question, even though Exact Sciences Corporation has indicated it has developed a new “Version 2” of the test that it believes will be superior to Version 1.1. The commenter suggests that CMS wait to reach a coverage decision on the test until appropriately documented scientific evidence is available for the new version of the test.

Another commenter who supports coverage wrote that “work in our lab is currently focused on developing a new generation of tests for the detection of adenomas and early stage cancers based on a technology called ‘BEAMing’.” The commenter suggests that “Broad coverage of fecal DNA testing as a class of test would help foster the development of clinically superior tests and the automation to ensure increasing efficiency in the laboratory.”

Comments without Evidence

CMS received 140 comments without references and citations to clinical evidence. Only one commenter in this category opposed coverage and one commenter did not express a preference relative to coverage because of the pending American Cancer Society national guidelines that have yet to be published.

Physicians

CMS received comments without evidence from 20 physicians. All of these commenters supported coverage of the test except for one. Many of the commenters indicated there is a general consensus that screening reduces colorectal cancer mortality and that the most effective means of doing that is screening individuals before there are any symptoms of a problem. These commenters stated that despite this consensus fewer than 50% of Americans over age 50 who are at risk for this cancer are being screened. They suggested that to increase this percentage there is a need for a more accurate, user-friendly screening test such as the stool DNA test. The only commenter in this category opposed to coverage indicated that the test "lacks added benefit and adds to a confusing set of options."

Other Health Care Professionals

CMS received comments without evidence from 32 other health care professionals. This category included individuals within the health care industry such as nurses, professors, researchers, consultants, advocacy groups, providers, corporate health directors, etc. All commenters supported coverage of the new test. One commenter indicated that there is a need for a "variety of options as there is never going to be a one-size-fits-all solution." Another commenter noted that "the vast majority of my patients refuse to undergo screening colonoscopies after the risks are explained to them." Additionally, one commenter said that "If screening rates are to increase for African American women and men, we need tests that are accessible, convenient and cost-effective."

General Public

CMS received 88 comments from the general public, including patients, screening candidates, their families and other individuals with an interest in the prevention or early detection of colorectal cancer. All of these commenters supported coverage of the new test. One described the stool DNA test as a "very simple solution for a major health concern in our country." A second stated that such a noninvasive alternative would "likely result in my being screened more often." Other commenters offered statements such as "I know my parents would be more likely to accept this stool test that can be collected in their home" and "I would use it if approved by Medicare....because of its convenience and simplicity."

VII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage.

For purposes of this scope of benefit NCD, the underlying authority for the colorectal cancer screening benefit is under § 1861(pp)(1)(D). Under our final rules effective March 1, 2003, the Secretary has modified the scope of the benefit to include "other tests or procedures established by a national coverage determination, and modifications to tests under this paragraph, with such frequency and payment limits as CMS determines appropriate, in consultation with appropriate organizations," as provided in 42 CFR 410.37(a)(1)(v). 67 Fed. Reg. 79966, 80040 (December 31, 2002). In view of the request from Exact Sciences for coverage of their test every 5 years as an alternative to a screening colonoscopy that may be covered every 10 years or as an alternative to a screening flexible sigmoidoscopy that may be covered every 4 years for average risk individuals, we are using the national coverage determination authority under 42 CFR 410.37(a)(1)(v) to determine whether the scope of the CRC screening benefit should be expanded to include the DNA stool test.

During our analysis of this test, an unexpected event occurred that profoundly affects market availability of the technology. In October 2007, the FDA stated that the PreGen-Plus™ test is a medical device that requires FDA clearance or approval prior to marketing (Appendix A). In December 2007, CMS received a letter from Exact Sciences describing the current situation and requesting a withdrawal of their initial request. This lack of availability of the test profoundly affects our assessment of it. In the absence of an FDA determination, CMS believes that there may be unresolved questions regarding the safety and effectiveness of the stool DNA test.

Since there is no FDA cleared or approved, commercially available stool DNA test for CRC screening at this time, CMS does not believe that identification of stool DNA mutations is an appropriate CRC screening test. Therefore, CMS proposes not to expand the colorectal cancer screening benefit to include coverage of this test. After a commercially available stool DNA test is cleared or approved by the FDA, a request for reconsideration would be anticipated.

VII. Proposed Decision

On August 1, 2007, we initiated the national coverage determination (NCD) process by opening a tracking sheet for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N). CMS proposes not to expand the colorectal cancer screening benefit to include coverage of this test because the FDA has determined that the only commercially available test, PreGen-Plus™, requires premarket review. We will consider a request for reconsideration when a commercially available stool DNA test has been cleared or approved by the FDA.

We are requesting public comments on this proposed determination pursuant to Section 1862 (I) of the Social Security Act. After considering the public comments and any other additional evidence, we will make a final determination and issue a final decision memorandum.

[Appendix A](#) [PDF, 85KB]

¹ The coverage of screening colonoscopy was expanded by the Benefits Improvements and Protection Act of 2000 to include beneficiaries at average risk every 10 years, effective January 1, 2002. Public Law No. 106-554, § 103 (2000).

² Individuals at high risk for colorectal cancer means an individual with (1) a close relative who has had colorectal cancer or adenomatous polyp; (2) family history of familial adenomatous polyposis; (3) family history of hereditary nonpolyposis colorectal cancer, (4) personal history of adenomatous polyps; (5) personal history of colorectal cancer; or (6) inflammatory bowel disease, including Crohn's disease and ulcerative colitis. See § 1861(pp)(2) of the Social Security Act.

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